



Corres and Mail
BOX AF

RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE
ART UNIT 1805

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Paul R. Schimmel

Serial No.: 08/249,689

Group Art Unit: 1805

Filed: May 26, 1994

Examiner: John Brusca

For: DESIGNING COMPOUNDS SPECIFICALLY INHIBITING RIBONUCLEIC
ACID FUNCTION

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

RECEIVED
JUL 25 1996
GROUP 1800

#34
M.G.J.
7/25/96
184

RESPONSE TO OFFICE ACTION
UNDER 37 C.F.R. § 1.116

Sir:

Responsive to the Office Action mailed on April 17, 1996, please consider the following comments.

The present application is directed to a method and compounds for inhibiting RNA function. Compounds are designed that bind to nucleotides exposed on the surface of the minor groove of the targeted RNA molecules. The presence of the compound within the minor groove inhibits RNA function.

In the Office Action mailed April 17, 1996, the Examiner withdrew the rejection under 35 U.S.C. § 112, second paragraph, and maintained the rejection under 35 U.S.C. § 112, first paragraph. The latter rejection was maintained for the reasons set forth in the Office Action mailed August 29, 1995. Claims 1 and 3-21 stand rejected under 35 U.S.C. §112, first paragraph, on the basis that the claims were not enabled by the specification. Applicant respectfully traverses this rejection.

Based on the Office Action mailed August 29, 1995, the present rejection appears to be based on a holding that it would require undue experimentation to practice the claimed method. That Office Action analyzes the claims and disclosure as suggested in *Ex parte Forman*, 230 USPQ 546 (Bd. App. 1986). In making this analysis, the rejection makes numerous assertions and conclusions regarding the various factors to be considered and bases these assertions and conclusions on certain evidence or argument. In the Amendment and Response mailed January 2, 1996, applicant attempted to point out where, in the chain of reasoning leading to the conclusion of undue experimentation, the evidence or reasoning was weak, non-existent, or contradictory. In the Office Action mailed April 17, 1996, the rejection responds by subtly misinterpreting applicant's intended arguments and continuing to improperly place the burden of proof on applicant.

Applicant submits that an analysis of whether undue experimentation is required to practice an invention involves a complicated weighing of several factors. Applicant asserts that in analyzing the factors, the Patent Office is initially burdened with establishing, through

evidence or convincing argument, that it would require undue experimentation to practice the claimed invention. In this regard, it is well established that absent such evidence or reasoning, the objective truth of statements made in the specification are to be accepted.

As stated in the Office Action mailed August 29, 1995, factors to be considered in determining whether undue experimentation is required include (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill level of those in the art; (g) the predictability of the art; and (h) the breadth of claims.

The Case for Undue Experimentation

After discussing these factors, the rejection makes essentially the following analysis (page 6, Office Action mailed August 29, 1995):

- (1) the skilled practitioner would initially look to the specification for guidance in practicing the invention;
- (2) the specification does not provide sufficient guidance;
- (3) the practitioner would then be required to look to the prior art;
- (4) the prior art contains neither methods of producing inhibitory compounds that bind to the minor groove nor examples of such compounds;
- (5) the practitioner would be forced to use empirical trial and error to produce inhibitory compounds that bind to the minor groove; and

(6) such trial and error experimentation represents undue experimentation.

Applicant initially notes that were it necessary to reach points (5) and (6), such experimentation might be undue. However, applicant has provided a method which will prevent those of skill in the art from having to resort to such trial and error. The conclusion that undue experimentation would be required to practice the invention is based on conclusions (2) and (4) in the above-cited analysis.

The Amount of Guidance Presented

The rejection states that conclusion (2) -- that the specification does not provide sufficient guidance -- is based on the discussion of enablement factors earlier in the rejection. In the discussion of enablement factors, the rejection makes essentially the following analysis of the guidance provided in the specification:

(i) the amount of direction or guidance presented in the specification is limited to citations and discussions of prior art;

(ii) the application does not distinctly describe procedures to perform any of the steps of the method (in particular determination of secondary and tertiary structure and synthesis of a compound that will bind to a critical site in the RNA¹);

(iii) no guidance is given for the therapeutic use of a compound produced by the method of the invention;

¹The rejection asserts that the steps of the method require, inter alia, demonstrating that the synthesized compound can be used therapeutically. However, the claims require no such demonstration.

- (iv) eight working examples are presented in the specification;
- (v) the working examples are "not drawn to the claimed method because the examples fail to demonstrate all steps of the method";
- (vi) no example is given of the design or the existence of a compound that inhibits the function of an RNA molecule by binding to its minor groove; and
- (vii) no example is given of a therapeutic use of a compound produced by the claimed method.

Applicants assert that this analysis is insufficient to support conclusion (2) above because these statements are variously incorrect, irrelevant, of insufficient weight, and/or are not dispositive of the question at hand. Applicant initially asserts that statement (i) is incorrect since the specification contains more than just prior art references and discussion. Applicants respectfully request that the prior art nature of all guidance, as alleged, be specifically pointed out in the next communication for the Patent Office. Applicant next notes that it is not clear how the form in which guidance is provided in the specification indicates anything about whether such guidance is sufficient for enablement. Applicant also notes that guidance in the form of reference to prior art knowledge and procedures is a legitimate form of guidance. In this regard, applicants respectfully request an explanation of why reference to the prior art necessarily indicates that such guidance is insufficient. In support of applicant's extensive citation of prior art, applicant notes that each of the steps in the claimed method represents determinations which have been performed, in isolation or in

partial combination, on numerous RNA molecules. The specification refers to many such examples and indicates that the procedures to be performed can be performed routinely by those of skill in the art. Applicant's invention lies in the recognition that (1) critical sequences in RNA molecules are useful sites for inhibiting function, and (2) these separate established procedures could be combined to provide a means of designing such inhibitory compounds. Thus, for the present invention which represents a new combination of procedures -- which when performed together as claimed and for the claimed purpose results in a useful method -- it is entirely appropriate to provide the bulk of guidance for practice of the invention through reference to prior art procedures.

In regard to statement (ii), applicant asserts that the specification does describe the procedures for performing steps of the method. In fact, the specification provides extensive guidance for performing the steps of the claimed method. Specifically, procedures for determination of critical sequences in RNA are described at least on pages 9-18, with an overview of RNA mutagenesis analysis for determination of critical sites presented on page 9, methods of synthesizing mutant RNAs for analysis presented on pages 9-12, and specific examples of analysis of critical sites on tRNA presented on pages 12-18. Procedures for determination of the primary, secondary, and tertiary structure of RNA molecules were well known at the time of filing and are referred to on pages 7-8. Examples of molecules which interact with specific RNA sequence structures are provided on pages 18-22. Such examples provide guidance for the choice of structures which can interact with a critical site on an

RNA molecule. Procedures for modeling such structures, and their interactions with RNA are provided on pages 37-38. Procedures for synthesizing RNA-specific compounds are provided on pages 38-39. In view of this, it is not clear what the PTO finds lacking. To the extent that statement (ii) is based on an implicit requirement that the specification present guidance in a particular form, applicant disputes this for the reasons discussed above. To the extent that statement (ii) was intended to constitute evidence that the specification provides insufficient guidance, applicant asserts that it fails to do so because the statement is conclusory without reference to support for the conclusion reached, and there is no argument presented establishing how the alleged lack of distinct description of method steps constitutes a lack of guidance in the context of the claimed invention.

In regard to statement (iii), applicant submits guidance is provided for the therapeutic use of compounds produced by the claimed method (see, for example, pages 39-41). Notwithstanding this, applicant notes that the claims *do not require any therapeutic effect* of such compounds. In this regard, it is noted that claim 1 requires only the design of a compound specifically inhibiting a targeted ribonucleic acid function. Accordingly, statement (iii) is both incorrect and not germane to the question of enablement of the claimed invention.

In regard to statement (iv), applicant agrees that the specification has eight numbered working examples. However, the specification also describes numerous other examples of individual steps in the claimed method, and examples of specific interactions of molecules

with RNA molecules. In this regard, applicant again emphasizes that the claimed method is a combination of procedures known in the art and for which examples of application of such procedures are known and described in the specification.

In regard to statement (v), applicant notes that the rejection fails to establish how the absence of a single complete working example, using all of the steps of the claimed method, prejudices enablement. Applicant asserts that the rejection implies that the lack of such a "complete" example weighs against enablement. As discussed above, however, due to the nature of the claimed invention (i.e. the new combination of known and established procedures), applicant submits that examples drawn to individual steps represent, collectively, a strong exemplification of the claimed invention. No reasoning has been provided as to why it matters that the invention is exemplified in a composite manner.

In regard to statement (vi), applicant notes that extensive guidance is provided for the design of inhibitory compounds (see, for example, pages 37-38, and the discussion of known examples of compounds which interact with RNA on page 18-22). Applicant respectfully points out that, to the extent that molecules are known which bind to specific critical sites in RNA molecules (such as portions of proteins responsible for specific RNA binding), examples of the required compounds exist which can be adapted for the design of new compounds according to the claimed method.

In regard to statement (vii), applicant again notes that the claims do not require any therapeutic effect and so the presence or absence of examples of such a therapeutic effect is not germane to the question of enablement.

In view of the incomplete, incorrect, and undeveloped nature of the "evidence" of lack of guidance presented in the rejection, as discussed above, and the fact that extensive guidance for the procedures necessary to practice the claimed invention appears in the specification, applicant asserts that this factor weighs heavily in favor of enablement.

The State of the Prior Art

The rejection states that conclusion (4) -- that the prior art does not provide methods for producing inhibitory compounds -- is based on the discussion of the prior art earlier in the rejection. In the discussion of the prior art, the rejection makes essentially the following analysis of the prior art:

- (i) relatively little progress has been made towards generating compounds that specifically interact with critical sites on RNA molecules;
- (ii) a survey of the prior art does not reveal examples of drugs that inhibit RNA molecules by binding to the minor groove;
- (iii) Some publications cited in the specification involving compounds which bind to nucleic acids or nucleotides do not indicate that the molecules bind to the minor groove of RNA or to nucleic acids.

(iv) Wilson *et al.*, *Biochemistry* 32:4098-4104 (1993), published three years after the priority date, was cited as indicating that no classes of small molecules binding to the minor groove of RNA have been defined by that time.

In regard to points (i), (ii), and (iv), applicant notes that the prior art did not have applicant's method and it is not clear what efforts had been made to obtain compounds specifically binding to the minor groove of RNA. Applicant notes that the prior art was clearly able to design and study compounds that interact with bases in nucleotides (see discussion below). Wilson *et al.* describe *initial* efforts, apparently started years after the present invention was made, to identify compounds that interact specifically with RNA. In addition, Wilson *et al.* describes not efforts to design such compounds, but a screening of compounds with known interactions with *DNA*. The probative value of the comment by Wilson *et al.* that no classes of small molecules have been defined that bind strongly to the minor groove of RNA has not been established insofar as Wilson *et al.* does not characterize any attempts to design such molecules. Similarly, the probative value of the comment by Wilson *et al.* that there are no outstanding paradigms to suggest design directions for RNA groove-binding drugs is in serious doubt because the present application, unknown to Wilson *et al.*, describes such a paradigm. Furthermore, this belief expressed in Wilson *et al.* that no such paradigm exists indicates that Wilson *et al.* was unaware of any systematic effort to *design* compounds that interact with RNA molecules based on any paradigm such as the one conceived by applicant. Thus, the alleged failure to produce such compounds contained in

Wilson *et al.* carries little weight regarding any alleged difficulty in practice of the present invention.

In regard to point (iii), Yamada *et al.*, *Nucleic Acids Research* 8:5767-5777 (1980), and Wank *et al.*, *J. Mol. Biol.* 236:1001-1010 (1994), were criticized in the rejection as failing to show that tuberactinomycin binds to the minor groove of RNA. Rebek *et al.*, *J. Am. Chem. Soc.* 109:5033-5035 (1987), Jeong and Rebek, *J. Am. Chem. Soc.* 110:3327-3328 (1988), and Askew *et al.*, *J. Am. Chem. Soc.* 111:1082-1090 (1989), were criticized in the rejection as discussing interaction of synthetic molecules with purines and pyrimidines rather than nucleic acids. Applicant initially notes that at least Askew *et al.* does discuss interaction with nucleic acids (see Scheme II, page 1087). Another publication cited in the specification (and of record), Rebek, *Science* 235:1478-1484 (1987), discusses compounds which can be used to bind to the major and minor grooves of nucleic acids (see paragraph bridging pages 1482 and 1483). Applicant submits that these publications clearly indicate that compounds were known with specific interactions with nucleic acids, and that structural basis for these interactions were known in detail. The authors of each of these publications were clearly conversant with the principles of the design of compounds having specific molecular interactions. Applicant asserts that this state of the art (and this level of skill and knowledge in the art) clearly supports enablement of the present claims. The concepts, techniques, and knowledge necessary to produce specifically interacting compounds were known. What is lacking in the prior art is the proper combination of techniques, and the

direction in which to apply them, which is provided by applicant's invention as described in the specification. Accordingly, applicant asserts that the state of the prior art was sophisticated enough to allow design of compounds which bind to critical sites in RNA without the need for undue experimentation. In this regard, applicant notes that no reasoning has been presented as to why or how undue experimentation would be required in view of the state of the prior art.

Other Factors

As for the other factors to be considered in determining whether undue experimentation is required, although these were discussed in the rejection, it is not clear how or if they were considered in arriving at the conclusion that undue experimentation would be required since they are not referred to in the analysis on page 6 of the Office Action mailed August 29, 1995. It is noted that the rejection admits that some factors favor enablement. For example, the rejection notes that the level of skill in the art is high and admits that the structure and location of critical sites of a number of RNA molecules have been successfully characterized in the prior art. The rejection also mischaracterizes several of the other factors. For example, the rejection states that the nature of the invention is the design of compounds with therapeutic utility which inhibit the function of an RNA molecule by binding to the minor groove. In fact, the claims do not require that the compounds have a therapeutic utility. The rejection asserts that it is not predictable which nucleotides are critical for function in an RNA molecule. While this may be true *a priori*, the invention

requires, and the specification describes, predictable procedures for determining the location of critical sites. That is, the procedure of determining which sites are critical can be performed as described in the specification with predictable results (i.e. the location of critical sites will be determined). The rejection also fails to characterize the amount of experimentation required. Accordingly, the other factors to be considered do not clearly support a conclusion that undue experimentation would be required to practice the claimed invention.

It appears from the lack of support for most bases offered for the present rejection (see discussion above), and the rebuttal offered in the Office Action April 17, 1996, that the crux of the present rejection is the question of whether or not it would require undue experimentation to actually design a compound that would bind to a critical site within the minor groove of an RNA molecule, thereby inhibiting the RNA function for which the site is critical. In support of the conclusion that undue experimentation would be required for those of skill in the art to effect such a design, the rejection notes that no such compounds are presented and that such compounds were not being produced three years after the priority date of the present application. Applicant agrees that these factors are relevant to the determination of whether undue experimentation would be required. However, applicant submits that more than this is required to establish that undue experimentation would be required and thereby support a *prima facie* case of lack of enablement. The Patent Office bears more of a burden than just listing such factors. In this regard, applicant notes that

arguments in the Office Action mailed April 17, 1996 clearly imply that, in making the present rejection, the Patent Office improperly considers it to be applicant's burden to provide evidence in the prior art or specification that the claimed method can be practiced. In fact, the objective truth of statements in the specification that such compounds can be designed is to be believed unless evidence or convincing reasons to doubt them are presented. In the present case, all that has been presented is a lack of evidence that compounds binding to the narrow groove of RNA have been produced. No evidence and no convincing argument has been presented that such design could not be accomplished. Without this, applicant submits, no *prima facie* case of lack of enablement has been established.

Notwithstanding the above argument, applicant has previously submitted a Declaration of Dr. Paul R. Schimmel Under 37 C.F.R. §1.132 (mailed July 28, 1992) in which Dr. Schimmel, an expert in the art of the analysis of RNA structure and rational design of compounds, and an expert in the knowledge of those of skill in this art, indicates that those of skill in the art at the time the invention was made could routinely design compounds binding to RNA given knowledge of the structure of the site of binding. Accordingly, absent evidence or convincing argument to the contrary, this aspect of the claimed method could be practiced without the need for undue experimentation.

Applicant respectfully submits that, for all of the foregoing reasons, the present claims meet the standards of 35 U.S.C. § 112, first paragraph.

U.S.S.N. 08/249,689
Filed: May 26, 1994
37 C.F.R. § 1.116 RESPONSE TO OFFICE ACTION

Allowance of claims 1 and 3-21 is respectfully solicited.

Respectfully submitted,



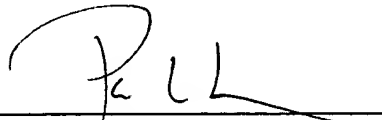
Patrea L. Pabst
Reg. No. 31,284

Date: July 17, 1996

ARNALL GOLDEN & GREGORY
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3400

Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.



Patrea Pabst

Date: July 17, 1996

Appendix

1. A method for designing a compound specifically inhibiting targeted ribonucleic acid function comprising the steps of:

- (a) determining the nucleotide sequence in the targeted ribonucleic acid that is critical to function;
- (b) determining the secondary structure of the region of the targeted ribonucleic acid in which the critical site is located;
- (c) determining the three-dimensional structure of the targeted RNA, including the position of the critical site relative to the major and minor grooves;
- (d) determining the sequence of nucleotides and structure flanking the critical site in the targeted ribonucleic acid that is specific to the critical region of the ribonucleic acid to be inhibited and within the minor groove; and
- (e) synthesizing a compound that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid thereby inhibiting targeted ribonucleic acid function.

3. The method of claim 1 wherein the ribonucleic acid is selected from the group consisting of mRNA, rRNA, tRNA and viral RNA.

4. The method of claim 1 wherein inhibition of targeted ribonucleic acid function inhibits protein synthesis.

5. The method of claim 4 wherein protein synthesis is inhibited in cells selected from the group consisting of tumor cells, virally infected cells, and bacterial cells.

6. The method of claim 1 wherein the three-dimensional structure is modeled using sequences of the RNA and calculating the minimum energies for these structures.

7. The method of claim 1 wherein the critical region of the targeted ribonucleic acid is determined by mutation of regions of the targeted RNA and comparison of the function of the mutated RNA with the original RNA, wherein mutations that result in mutant RNA having altered function indicate that the site of mutation is a critical site.

8. The method of claim 1 wherein the targeted RNA is a tRNA, wherein the critical region of the tRNA is determined by site directed mutation of the tRNA and analysis of the function of the mutated tRNA.

9. The method of claim 1 further comprising determining an effective amount of the compound and combining the compound with a pharmaceutical carrier.

10. The method of claim 9 wherein the carrier is selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

11. A compound specifically binding to and inhibiting the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

13. The compound of claim 11 further comprising a pharmaceutically acceptable carrier selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

14. The method of claim 3 wherein the critical site is in the minor groove of the acceptor stem of a tRNA molecule.

15. The method of claim 14 wherein the tRNA molecule is tRNA^{Ala}.

16. The method of claim 15 wherein the critical site is the G3:U70 base pair.

17. The compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

U.S.S.N. 08/249,689

Filed: May 26, 1994

37 C.F.R. § 1.116 RESPONSE TO OFFICE ACTION

18. The compound of claim 17 wherein the tRNA molecule is tRNA^{Ala}.
19. The compound of claim 17 wherein the critical region is the G3:U70 base pair.
20. The method of claim 1 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.
21. The compound of claim 11 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.

In re application of: Paul R. Schimmer

Serial No.: 08/249,689

Filed: May 26, 1994

For: DESIGNING COMPOUNDS SPECIFICALLY INHIBITING RIBONUCLEIC ACID FUNCTION

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

RECEIVED

JUL 25 1996

GROUP 1800

- ☒ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.
- ☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.
- ☒ No additional fee is required.

The fee has been calculated as shown below:

(Col. 1)			(Col. 2)	(Col. 3)	SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDIT. FEE	RATE	ADDIT. FEE
TOTAL	20	MINUS	20	= 0	X 11 =	\$ 0	x22=	\$
INDEP	2	MINUS	3	= 0	x 39 =	\$ 0	x78 =	\$
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+125	\$	+250	\$
					TOTAL ADDIT. FEE	\$ 0	or	TOTAL
								\$

* If the entry in Col.1 is less than the entry in Col.2, write "0" in Col.3.

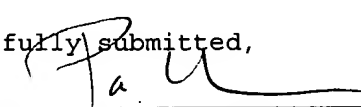
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col.1 of a prior amendment or the number of claims originally filed.

- ☐ Please charge my Deposit Account No. 01-2507 amount of \$. A duplicate copy of this sheet is attached.
- ☐ A check in the amount of \$ is attached.
- ☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 01-2507. A duplicate copy of this sheet is attached.
- ☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.
- ☒ Any patent application processing fees under 37 CFR 1.17.

Respectfully submitted,


 Patrea L. Pabst, Reg. No. 31,284